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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,562	11/14/2001	Avi J. Ashkenazi	P2730P1C18	2836

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,562	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-121 and 123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-121 and 123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Part III: Detailed Office Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/18/2006 has been entered.

Claims 119-121 and 123 are pending and under consideration. The claims are drawn to antibodies that bind PRO1111 protein.

IDS:

The information disclosure statement, filed 1/18/2006, has been considered.

Priority Determination:

The utility for the claimed protein is active in a chondrocyte redifferentiation assay. Applicants have established that the PCT application contains the chondrocyte redifferentiation. Accordingly, priority is set at 3/30/00.

Applicants argument that priority is merited to 6/23/1999 has been fully considered but is not deemed persuasive This argument has been fully considered but is not deemed persuasive for reasons cited below:

At page 3-4, applicants reiterate the argument that amplification of the *gene* encoding the proteins bound by the claimed antibodies in seven lung tumors and four colon tumors establishes that it is more likely than not that the claimed antibodies can be used as a cancer diagnostic. This argument has been fully considered but is not deemed persuasive because it is an incomplete and misleading characterization of the data in the specification. According to the specification at

page 552-553, seven of nineteen lung tumor cell lines and four of seventeen colon tumor cell lines tested positive. However, it remains that the amplification was minimal, and that the most parsimonious explanation is aneuploidy, with no evidence that the chromosome bearing PRO1111 was preferentially amplified (as opposed to other chromosomes). Aneuploidy is also a feature of damaged tissue, and is commonly found in colon and lung tissues, which are subject to environmental damage. It does not invariably or inevitably lead to cancer; rather, such damaged cells are generally removed by the body via apoptosis; the development of cancer is the exception, as evidenced by the fact that the general population is constantly suffering damage to lung cells via air pollution, whereas lung cancer remains relatively rare. Further, it remains that the 2-3 fold amplification of the nucleic acid is consistent with a simple case of aneuploidy, in which there is a single extra copy of the chromosome in question, and is *not* predictive of a similar differential in protein expression; hence, the argument is not persuasive, as the claims are drawn to polypeptides, not the nucleic acids that encode them. Merely because amplification *may* be an *initial* step in the formation of cancer does not equate with a substantial assertion of diagnostic utility for the encoded protein. There is no factual support for applicant's assertion at page 4 of the response that "it helps in identifying individuals at *significantly increased cancer risk" (*emphasis added). Simply put, applicant's urged "more likely than not" standard is amply met

The Declaration by Dr. Goddard has been fully considered but is not deemed persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949).

It is noted that the declaration is one originally filed in application number 09/903925, and is dated 1/16/2003. Declarant discusses the accuracy of the Taq DNA polymerase assay, stating that the Taqman PCR technique is sensitive enough to detect at least a 2-fold increase in

gene copy number (paragraph 3) and that this increase is significant and useful. This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1111gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1111 *nucleic acid* was amplified in some cancers, to a minor degree (about 2-3 fold). No mutation or translocation of PRO1111 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1111 is expressed in corresponding normal tissues, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1111 is amplified in a variety of samples, including some normal tissues, and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" is associated with any change in protein expression, nor whether the protein was expressed in *any of the tissues at all.* It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only Doctor Goddard's conclusions are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants argument of the Pennica reference at page 6 of the response has been fully considered but is not deemed persuasive. Applicants have plucked a single phrase from the portion cited by the Examiner, which phrase supports their assertion of utility. However, they

have taken that phrase out of context; the teachings of Pennica as a whole support the opposite conclusion, that utility of the polypeptide cannot be predicted based upon amplification of the nucleic acid, for reasons set forth in the office action mailed 7/1/2004.

Applicant argues at pages 6-7 that the Examiner has improperly generalized the teachings of Pennica and Konopka. This argument has been fully considered but is not deemed persuasive because both references are cited to establish the state of the art, which is that it is not predictable that a protein will be significantly amplified based upon a minor amplification of the nucleic acid encoding it. It is necessary to cite specific examples to form a general argument.

At pages 6-7, applicants argue that the Haynes reference establishes a general trend, and that few data points deviated from the expected, and thus that Haynes shows that the data meet a "more likely than not" standard of predictability. This argument has been fully considered but is not deemed persuasive because Figure 1 of Haynes, argued by applicants, shows data correlating *protein and mRNA* levels, not genomic DNA levels and protein. Applicants have not provided any mRNA data for PRO1111. Only DNA levels are provided, no mRNA or protein levels. Accordingly, the data in the specification as filed cannot be correlated with those of Haynes. Further, the figure clearly has a tight cluster of data points showing little or not protein expression at the region corresponding to 2-3 copies of mRNA. However, the principle for which Haynes was originally cited by the Examiner still applies: Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). That is Haynes' conclusion, not the Examiner's. The 'general trend' pointed to by applicants is seen at a level of mRNA copy number that has not been established for PRO1111, nor is it predictable from the observation of 2-3 copies of *DNA* per cell.

It is noted that all the references cited by the Examiner appeared in peer-reviewed publications. Applicants repeatedly try to impugn the statistical methods used therein, by general allegation. The Examiner finds no merit in this argument.

Applicants arguments pertaining to the Orntoft, Hyman and Pollack references remains not persuasive for reasons of record. Orntoft et al. *could only compare the levels of about 40 well-resolved and focused abundant proteins."* (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of

amplification of DNA, found only in a minority of tested tumors which were not characterized on the basis of those in the Ornoft publication, and an associated rise in level of the encoded protein. The Hyman reference cited by applicants found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of SEQ ID NO: 228 would be correlated with elevated levels of mRNA, much less the claimed protein. Further, Hyman does not examine protein expression. Applicants are reminded that the instant claims are directed to proteins. Similarly, Pollack, cited by applicants, does not analyze protein levels, nor does Pollack support the assertion that it is predictable, on the basis of the minimal increase in copy number of SEQ ID NO: 228 that the protein would accordingly be found at altered levels. Accordingly, it remains that the significance of the gene amplification data is questionable, and cannot be predictably extrapolated as applying to the claimed protein. The art, taken as a whole, clearly teaches that it is not predictable that a two-fold copy increase in the nucleic acid would translate to detectable over-expression of the associated mRNA, much less any protein encoded thereby. Further, as evidenced by the Ornoft publication, the type of data presented in the instant specification clearly does not meet the standard in the art for establishing association of a protein with cancer.

The Polakis declaration was fully considered in the previous Office Action. No further comment is necessary.

It remains that the art considers that that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed antibodies is not in currently available form, the asserted utility is not substantial. Applicants arguments to the contrary fail to meet the urged "more likely than not" standard, but rather fall well within the category that significant further experimentation would be required to

determine if the claimed polypeptides have the urged utility, experimentation of the type that was found to be impermissible by the court in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct,.1966).

The effective priority date remains set at 3/30/2000.

Rejections Over Prior Art:

Priority is set at 3/30/00.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 119-121 remain rejected under 35 U.S.C. 102(a) as being anticipated by Jacobs, WO 99/50405. SEQ ID NO: 2 of the publication is 99.7% identical to SEQ ID NO: 229 of the instant application. Antibodies are disclosed beginning at page 77, and include monoclonal, polyclonal, humanized, chimeric, and single chain antibodies. At page 78 the disclosure states that the antibodies may be used for detection of protein. Accordingly, the claims are anticipated by Jacobs. Applicants argument pertaining to the priority date in the paper filed 1/13/2006 is not persuasive for reasons cited above with respect to priority date determination.

Claims 119-121 and 123 remain rejected under 35 U.S.C. 102(e) as being anticipated by Shimkets, U.S. Patent Number 6,689,866 or US Patent Application Publication US2003/0054514 A1, or US Patent Application Publication US2003/0003532 A1. The US Patent Application Publications are divisionals of the patent, and differ only in the claims. The '514 publication contains claims to nucleic acids, proteins (see claim 11), and antibodies (see claim 13), and the '532 application contains claims to nucleic acids and vectors. The teachings will be discussed with reference to the issued patent. SEQ ID NO: 9 of the patent is 99.7% identical to SEQ ID NO: 228 of the instant application, at bases 1-2183 (bases 159-2341 of the patent), and encodes a protein 99.2% identical to that of SEQ ID NO: 229. SEQ ID NO: 31 is a fragment of SEQ ID NO: 9, is identified as encoding the extracellular domain (see figures 17A and 17B), which is 100% identical to residues 45-495 of SEQ ID NO: 229. Antibodies are disclosed at column 36, and include monoclonal, polyclonal, humanized, chimeric, and single chain antibodies. Labeled antibodies are disclosed at column 37, lines 44-45. Accordingly, the claims are anticipated by Shimkets. Applicants argument pertaining to the priority date in the paper filed 1/16/2006 is not persuasive for reasons cited above with respect to priority date determination.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 119-120 and 123 remain rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al. for reasons cited in the previous Office Action mailed 7/1/2004, at page 7. Applicants argument pertaining to the priority date in the paper filed 1/16/2006 is not persuasive for reasons cited above with respect to priority date determination.

Claim 121 remains rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al. and further in view of U.S. Patent Number 5,565,332 (Hoogenboom et al.) in the case of claim 121, or in view of U.S. Patent Number 4,946,778 (Ladner et al.) in the case of claim 122 for reasons cited in the previous Office Action mailed 7/1/2004, at pages 7-8. Applicants argument pertaining to the priority date in the paper filed 1/16/2006 is not persuasive for reasons cited above with respect to priority date determination.

In further regard to the above two rejections, applicants argue at page 10 of the response that rejection of the claimed antibodies "based on nucleic acid EST's alone is not appropriate". This argument has been fully considered but is not deemed persuasive because the rejections are *not* made over "EST's alone", but rather in view of the teachings of the prior art, as evidenced by the Sibson reference. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim 123 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs, WO 99/50405 for reasons cited in the previous Office Action mailed 7/1/2004, at page 8.

Applicants argument pertaining to the priority date in the paper filed 1/16/2006 is not persuasive for reasons cited above with respect to priority date determination.

Advisory Information:

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner